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Clinical Outcomes After Traumatic Brain Injury and Exposure to Extracranial Surgery

A TRACK-TBI Study

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IMPORTANCE Traumatic brain injury (TBI) is associated with persistent functional and cognitive deficits, which may be susceptible to secondary insults. The implications of exposure to surgery and anesthesia after TBI warrant investigation, given that surgery has been associated with neurocognitive disorders.

OBJECTIVE To examine whether exposure to extracranial (EC) surgery and anesthesia is related to worse functional and cognitive outcomes after TBI.

DESIGN, SETTING, AND PARTICIPANTS This study was a retrospective, secondary analysis of data from the Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) study, a prospective cohort study that assessed longitudinal outcomes of participants enrolled at 18 level I US trauma centers between February 1, 2014, and August 31, 2018. Participants were 17 years or older, presented within 24 hours of trauma, were admitted to an inpatient unit from the emergency department, had known Glasgow Coma Scale (GCS) and head computed tomography (CT) status, and did not undergo cranial surgery. This analysis was conducted between January 2, 2020, and August 8, 2023.

EXPOSURE Participants who underwent EC surgery during the index admission were compared with participants with no surgery in groups with a peripheral orthopedic injury or a TBI and were classified as having uncomplicated mild TBI (GCS score of 13-15 and negative CT results [CT⁻ mTBI]), complicated mild TBI (GCS score of 13-15 and positive CT results [CT⁺ mTBI]), or moderate to severe TBI (GCS score of 3-12 [m/sTBI]).

MAIN OUTCOMES AND MEASURES The primary outcomes were functional limitations quantified by the Glasgow Outcome Scale-Extended for all injuries (GOSE-ALL) and brain injury (GOSE-TBI) and neurocognitive outcomes at 2 weeks and 6 months after injury.

RESULTS A total of 1835 participants (mean [SD] age, 42.2 [17.8] years; 1279 [70%] male; 299 Black, 1412 White, and 96 other) were analyzed, including 1349 nonsurgical participants and 486 participants undergoing EC surgery. The participants undergoing EC surgery across all TBI severities had significantly worse GOSE-ALL scores at 2 weeks and 6 months compared with their nonsurgical counterparts. At 6 months after injury, m/sTBI and CT⁺ mTBI participants who underwent EC surgery had significantly worse GOSE-TBI scores ($B = -1.11$ [95% CI, -1.53 to -0.68] in participants with m/sTBI and -0.39 [95% CI, -0.77 to -0.01] in participants with CT⁺ mTBI) and performed worse on the Trail Making Test Part B ($B = 30.1$ [95% CI, 11.9 - 48.2] in participants with m/sTBI and 26.3 [95% CI, 11.3 - 41.2] in participants with CT⁺ mTBI).

CONCLUSIONS AND RELEVANCE This study found that exposure to EC surgery and anesthesia was associated with adverse functional outcomes and impaired executive function after TBI. This unfavorable association warrants further investigation of the potential mechanisms and clinical implications that could inform decisions regarding the timing of surgical interventions in patients after TBI.

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Annually, at least 69 million people across the globe sustain traumatic brain injuries (TBIs),¹ and many have other injuries that warrant surgical evaluation. A Mayo Clinic study found that approximately 50% of patients with mild TBI (mTBI) had surgery within 1 week of injury, and 5% had procedures and anesthesia unrelated to the traumatic event that caused their mTBI.² On the basis of these studies, there are millions of patients worldwide who undergo procedures after TBI³ that could likely be delayed annually. At the same time, delays in surgery can worsen outcomes in some^{4,5} but not all situations.⁶ However, increasing evidence suggests that exposure to surgery and anesthesia may be detrimental to the brain. The proposition that surgery and anesthesia might have neurotoxic sequelae, albeit still controversial, has been demonstrated in children^{7,8} and older adults.^{9,10} To our knowledge, no studies have investigated the association between exposure to extracranial (EC) surgery and anesthesia and outcomes after TBI.

Posited mechanisms for the worsening of neurologic outcomes after surgery and anesthesia in participants with TBI include physiologic disruptions from the trauma itself, the surgical stress response,¹¹ or the anesthetic technique.¹² Secondary insults may result from physiologic derangements, including hypotension, anemia, hypoxia, hyperoxia, hyperglycemia, increased cerebral metabolic rate, decreased cerebral perfusion pressure or cerebral blood flow or autoregulation, neurotransmitter signaling, and disruption of blood-brain barrier integrity.¹³⁻¹⁵ Surgical techniques, although necessary to correct the traumatized anatomy, can also substantially affect variables, including lung function,¹⁶ intravascular distribution, and surgical stress.¹² Exposure to anesthesia may be both neuroprotective¹⁷ and neurotoxic for certain at-risk populations, such as pediatric participants, elderly individuals, or neurologically frail people,⁷⁻¹⁰ given that anesthetic mechanisms are heterogeneous¹⁸ and differentially affect the cerebral metabolic rate, cerebral perfusion pressure, and autonomic function,¹⁹⁻²² along with inflammatory, immunologic, and endocrine pathways.^{11,23-26}

The hypothesis of this study was that exposure to surgery, and consequently anesthesia, is associated with worsened indexes of brain injury as measured by functional and cognitive outcomes after TBI. Aggravated brain injury could decrease quality of life, delay recovery, and increase health care costs. This theory was tested using data from the Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) study²⁷ to compare patients who underwent EC surgery with patients with no surgery in the following injury groups: mild TBI (GCS score of 13-15 and negative computed tomography results; [CT⁻ mTBI]), complicated mild TBI (GCS score of 13-15 and positive CT results [CT⁺ mTBI]), moderate to severe TBI (GCS score of 3 to 12 [m/sTBI]), or peripheral orthopedic traumatic injuries (orthopedic trauma controls [OTCs]).

Methods

Study Population and Design

This study was a retrospective, secondary analysis of data from the TRACK-TBI study, a prospective, observational, cohort

Key Points

Question Are functional and cognitive outcomes worse after traumatic brain injury (TBI) in those exposed to extracranial surgery and anesthesia compared with unexposed people?

Findings In this cohort study of 1835 level I trauma center patients with broad TBI severity levels, extracranial surgery and anesthesia were associated with worse functional and cognitive outcomes at 2 weeks and 6 months after injury, especially in persons with acute intracranial findings on neuroimaging.

Meaning The findings support an association between exposure to extracranial surgery and anesthesia and worse outcomes after TBI in both functional and cognitive domains, suggesting that the perioperative period may be associated with detrimental effects on an injured brain.

study that assessed longitudinal outcomes of participants enrolled at 18 level I US trauma centers from February 1, 2014, to August 31, 2018. TRACK-TBI participants included TBI and OTC groups (eFigure 1 in Supplement 1). Patients with TBI presented within 24 hours of injury and had a head CT scan. Scan results were classified as positive according to the National Institute of Neurological Disorders and Stroke (NINDS) Common Data Element Neuroimaging Working Group consensus recommendations.²⁸ The OTC patients presented with orthopedic injuries without evidence of head trauma. All participants or their legally authorized representatives gave written informed consent. Inclusion criteria were known Glasgow Coma Scale (GCS) score and CT status, admission to the hospital, complete surgical record, and no intracranial operations. Extracranial surgery refers to all operations outside the skull and intracranial vault. Exclusions for TRACK-TBI included incarceration, pregnancy, nonsurvivable physical trauma, debilitating mental health disorders, neurologic disease, or not speaking English or Spanish. This analysis excluded individuals if they were younger than 17 years, were discharged home from the emergency department (ED), or had unknown GCS score on arrival at the ED. Additionally, individuals were excluded if any surgery was recorded as preinjury, any surgery type was unknown, or the only surgery was insertion of a tracheostomy tube, gastrostomy tube, or both. The TRACK-TBI study was approved by the institutional review board of each enrolling institution and led by the University of California, San Francisco. This study was completed in accordance with a Data Use Agreement between UCSF and the Medical College of Wisconsin as approved by the TRACK-TBI Executive Committee and the Medical College of Wisconsin Institutional Review Board. The study followed the Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Outcome Measures

Demographic, injury, and outcome variables were collected from the TRACK-TBI database in accordance with the TBI Common Data Elements through a combination of medical records, patient report, and direct assessment (eTable 1 in Supplement 1).^{29,30} These demographics were collected in accordance with the NINDS TBI Common Data Elements. The

source of data for race and ethnicity (participant report vs medical records) was not collected. Functional recovery from injury was quantified with the Glasgow Outcome Scale-Extended for all injuries (GOSE-ALL) and those limited to brain injury (GOSE-TBI) (range, 1-8; higher scores indicate a better outcome).^{31,32} Cognitive outcomes included neuropsychological assessments of executive functioning, processing speed, and memory. Executive functioning was quantified using the Trail Making Test Parts A and B (number of seconds to complete; part A, maximum score is 101 seconds; part B, maximum score is 301 seconds; lower scores indicate faster or better for both).³³ Processing speed was examined using the Wechsler Adult Intelligence Scale-Fourth Edition Processing Speed Index (WAIS-PSI; mean [SD] normative score, 100 [15]; higher scores indicate better processing speed).³⁴ Verbal episodic memory was tested using the Rey Auditory Verbal Learning Test (RAVLT; range for immediate recall, 0-80; range for delayed recall, 0-16; more correct indicates better memory).^{35,36} Outcomes were assessed for GOSE-ALL, GOSE-TBI, Trail Making Test Part A, Trail Making Test Part B, WAIS-PSI, RAVLT Immediate Recall (sum of trials 1-5; RAVLT score of 1-5), and RAVLT Delayed Recall/Long Delay (RAVLT-LD) at 2 weeks and 6 months after injury. Criteria for cognitive impairment on neuropsychological tests was performance below the ninth percentile based on demographically adjusted norms (ie, normative T score, ≤ 37 ; standard score, ≤ 79 ; and z score ≤ -1.33).

Statistical Analysis

Group compositions were defined and finalized before any analysis after a planned initial review of descriptive data determined that further winnowing (particularly m/sTBI; GCS 3-12) was not feasible due to sample size limitations ($n = 20$ in the EC surgery group with GCS scores of 9-12, $n = 54$ in the nonsurgical group with GCS scores of 9-12, $n = 78$ in the EC surgery group with GCS scores of 3-8, and $n = 102$ in the nonsurgical group with GCS scores of 3-8). Differences in demographic and clinical characteristics between the 2 surgery groups were assessed for statistical significance using Fisher exact tests for categorical variables and Mann-Whitney or Kruskal-Wallis tests for continuous and ordinal variables (Table 1). A fixed-effects linear regression model evaluated the association among injury group, surgery groups, and injury $\times$ surgery interaction, with each clinical outcome and each time point modeled separately (eMethods in Supplement 1). A sensitivity analysis was performed for the GOSE modeling at 2 weeks and 6 months in which deaths (GOSE = 1) before 2 weeks were excluded. A 2-sided threshold of $P < .05$ was used to determine statistical significance, with no adjustments for multiple comparisons. This analysis was conducted between January 2, 2020, and August 8, 2023.

Results

Participant Characteristics

Of the initial cohort of 2996 participants, 1161 were excluded, leaving 1835 (mean [SD] age, 42.2 [17.8] years; 1279 [70%] male and 556 [30%] female; 299 Black, 1412 White, and 96 other,

including Alaska Native/Inuit [$n = 1$], American Indian/Native American [$n = 5$], Asian [$n = 56$], Native Hawaiian/Pacific Islander [$n = 5$], and multiracial [$n = 29$]), including 1646 participants with TBI and 189 OTCs. There were 1349 nonsurgical participants and 486 participants undergoing EC surgery (Table 1). Altogether 89% of participants were discharged by 2 weeks after injury. Within the TBI group, the sample sizes with 2-week and 6-month outcomes were 988 to 1057 across 2-week outcomes and 902 to 1049 across 6-month outcomes. Within the OTC group, the sample size with 2-week outcomes was 118 to 139 and the sample size with 6-month outcomes was 102 to 123 participants (eFigure 1 in Supplement 1). The weighted nonsurgical and EC surgery groups were well balanced in age, educational level, race, injury cause, time to ED, and ED disposition (Table 1; eTable 2 and eTable 3 in Supplement 1). The EC surgery group underwent procedures primarily for extremity fracture (271 [56%]) or other EC injuries (146 [30%]). The EC operations performed within 24 hours of admission are listed in eTable 4 in Supplement 1.

Functional Outcomes

Figure 1 displays the GOSE-ALL and GOSE-TBI outcomes by group at 2 weeks and 6 months (eTable 5 in Supplement 1). Participants with m/sTBI had significantly worse outcomes on GOSE-TBI and GOSE-ALL compared with other groups at both times (eTable 6 in Supplement 1). At 6 months, planned comparisons found significantly lower GOSE-ALL scores in the m/sTBI and CT⁺ mTBI groups that underwent EC surgery compared with their nonsurgery counterparts (eTable 6 in the Supplement 1). In these groups, effect sizes ranged from -0.55 to -0.58 points ($P = .01$; Cohen $d = -0.39$ to -0.41). The GOSE-TBI was significantly lower by 0.47 points ($P = .03$; Cohen $d = -0.33$) in the CT⁺ mTBI group who underwent surgery.

Participants whose GOSE outcome was death within 2 weeks were excluded from a planned analysis to mitigate a selection bias of nonsurvivable injuries, withdrawal of care, or futility, which would skew the results toward the null hypothesis. After exclusion of deaths within 2 weeks, the GOSE-ALL scores were significantly lower in the surgery group compared with the nonsurgery group at 2 weeks (eTable 7 in Supplement 1) and 6 months (Table 2; eTable 8 in Supplement 1) within all groups. At 2 weeks, the GOSE-TBI score remained significantly lower in the CT⁺ mTBI group. At 6 months after injury, participants with m/sTBI and CT⁺ mTBI who underwent EC surgery had significantly worse GOSE-TBI scores (-1.11 [95% CI, -1.53 to -0.68] in participants with m/sTBI and -0.39 [95% CI, -0.77 to -0.01] in participants with CT⁺ mTBI) (Table 2).

Neurocognitive Outcomes

Neurocognitive outcomes were quantified using the Trail Making Test Parts A and B, WAIS-PSI, RAVLT Immediate Recall, and RAVLT-LD. Participants with m/sTBI had significantly worse outcomes on all neuropsychological tests at 2 weeks (eTables 7 and 9 in Supplement 1) and 6 months (Table 2; and Figure 2; eTable 8 and eFigure 2 in Supplement 1). When exposure to surgery was considered, participants with m/sTBI had significantly worse Trail Making Test Part B scores ($B = 30.1$ [95% CI, 11.9 - 48.2];

Table 1. Clinical and Demographic Characteristics of the Study Participants^a

Characteristic	Patient group		P value (surgery comparison) ^b	
	No surgery (n = 1349)	Extracranial surgery ^c (n = 486)	Unweighted	Weighted ^d
Injury group ^e				
m/sTBI	156 (12)	98 (20)	<.001	<.001
CT ⁺ mTBI	546 (40)	86 (18)		
CT ⁻ mTBI	579 (43)	181 (37)		
OTC	68 (5)	121 (25)		
GCS score, mean (SD) ^f	13.7 (3.0)	12.2 (4.4)	.03	.15
Age, mean (SD), y	42.7 (18.3)	40.6 (16.3)	.08	.12
Sex				
Male	914 (68)	365 (75)	.003	.002
Female	435 (32)	121 (25)		
Educational level, mean (SD), y	13.3 (3.0)	13.0 (2.8)	.02	.45
Race				
Black	222 (17)	77 (16)	.33	.68
White	1034 (78)	378 (80)		
Other ^g	77 (6)	19 (4)		
Hispanic ethnicity	273 (21)	120 (25)	.04	.27
Injury cause				
MVC occupant	409 (30)	159 (33)	<.001	.01
MCC	115 (9)	78 (16)		
MVC cyclist or pedestrian	178 (13)	64 (13)		
Fall	395 (29)	97 (20)		
Assault	95 (7)	11 (2)		
Other or unknown	157 (12)	77 (16)		
Lost consciousness	1087 (85)	316 (67)	<.001	<.001
PTA	959 (78)	250 (60)	<.001	<.001
ISS score, mean (SD)				
Total	11.3 (8.4)	15.5 (11.4)	<.001	.66
Peripheral	4.5 (5.9)	10.2 (8.3)	<.001	<.001
AIS peripheral score				
Mean (SD)	1.4 (1.1)	2.4 (1.0)	<.001	<.001
0	270 (21)	18 (4)		
1	489 (37)	57 (12)		
2	300 (23)	183 (38)		
3	210 (16)	177 (37)		
4	36 (3)	36 (7)		
5	2 (0)	10 (2)		
Shock index, ^h mean (SD)	0.65 (0.19)	0.69 (0.22)	.002	.16
Hemoglobin, ^h mean (SD), g/dL	14.1 (1.6)	13.8 (1.7)	.04	.23
SpO ₂ , ^h mean (SD), %	97.9 (2.7)	97.7 (3.3)	.75	.50
Base deficit, ^{h,i} mean (SD), mEq/L	2.7 (3.2)	3.8 (3.7)	.004	.06

Abbreviations: AIS, Abbreviated Injury Scale; CT⁺ mTBI, computed tomography-positive mild traumatic brain injury; CT⁻ mTBI, computed tomography-negative mild traumatic brain injury; GCS, Glasgow Coma Scale; ISS, Injury Severity Score; MCC, motorcycle crash; m/sTBI, moderate to severe traumatic brain injury; MVC, motor vehicle crash; OTC, orthopedic trauma control; SpO₂, oxygen saturation as measured by pulse oximetry.

SI conversion factors: To convert hemoglobin grams per liter, multiply by 10; base deficit to millimoles per liter, multiply by 1.

^a Data are number (percentage) of participants unless otherwise indicated.

^b Surgical comparison P value is for main effect of no surgery vs extracranial surgery contrasts for group totals (not based on injury severity).

^c Extracranial surgery refers to all operations outside the skull, including maxillofacial procedures. All participants who underwent intracranial procedures (ie, craniotomy) were excluded.

^d Weighted by inverse probability of injury group membership.

^e Cells that report percentages refer to the percentage within that column unless otherwise specified.

^f Mean (SD) GCS score was based on TBI groups only, not including the OTC group.

^g Other includes Alaska Native/Inuit, American Indian/Native American, Asian, Native Hawaiian/Pacific Islander, and multiracial.

^h First on admission within 24 hours assessed with shock index, hemoglobin, SpO₂, and base deficit.

ⁱ Base deficit data were mostly missing (1167 of 1349 [87%] in the nonsurgical group and 362 of 486 [74%] in the surgical group).

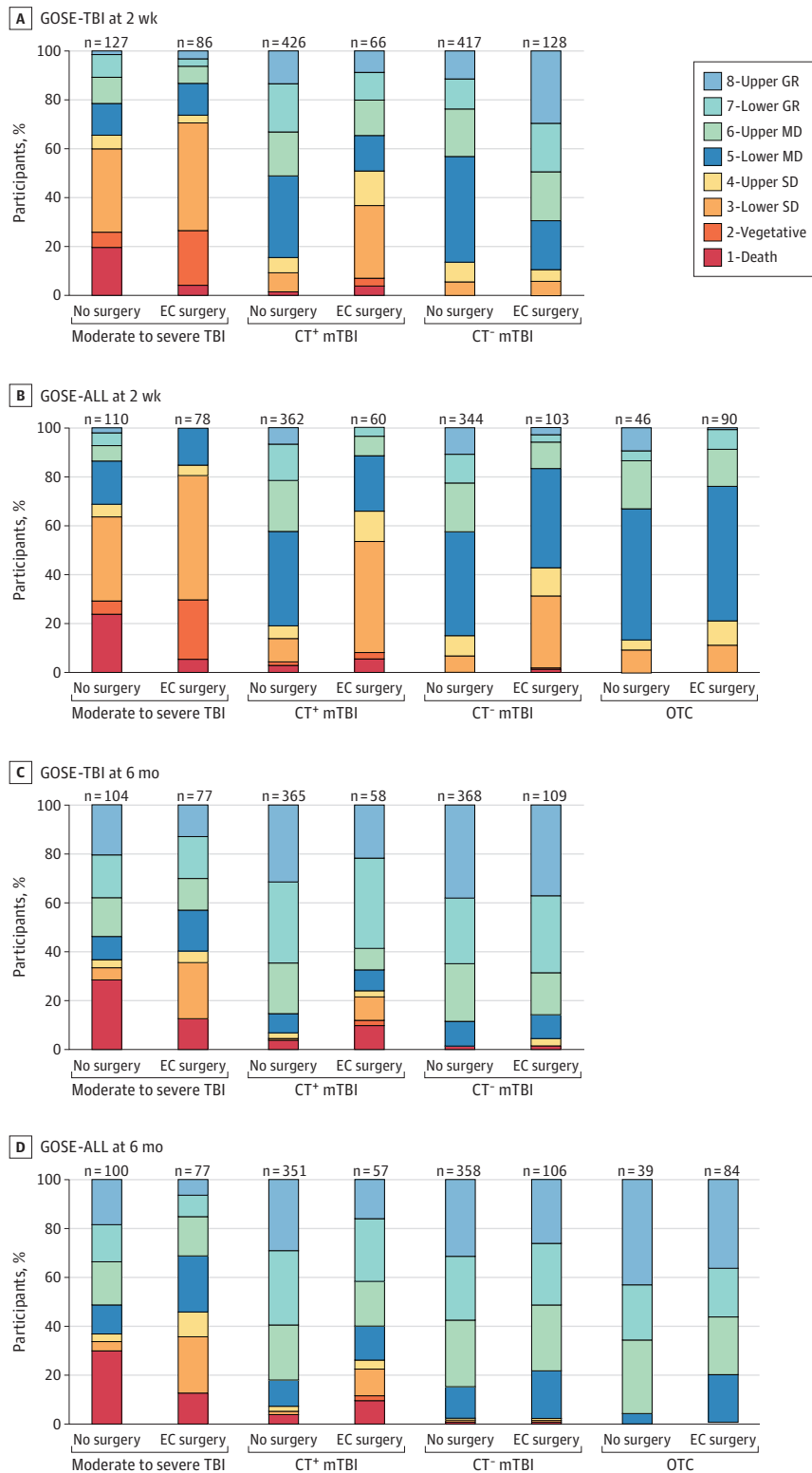
Cohen $d = 0.70$ [95% CI, 0.28-1.13]; $P = .001$) at 6 months compared with nonsurgical counterparts (Table 2). Participants with CT⁺ mTBI who underwent EC surgery scored significantly worse on the Trail Making Test Part B at 2 weeks ($B = 36.6$ [95% CI, 20.5-52.7]; Cohen $d = 0.77$; [95% CI, 0.43-1.11]; $P < .001$) and 6 months ($B = 26.3$ [95% CI, 11.3-41.2]; Cohen $d = 0.61$ [95% CI, 0.26-0.96]; $P = .001$) and the RAVLT-LD at 6 months (Cohen $d = -0.37$; $P = .04$) compared with nonsurgical counterparts. The percentage of each group who met clinical criteria for

impairment was quantified to provide additional descriptive data (eTable 10 and eFigure in Supplement 1; Figure 3).

Discussion

To our knowledge, this study is the first-in-human evidence demonstrating worse functional and cognitive outcomes associated with exposure to EC surgery and anesthesia after TBI.

Figure 1. Functional Outcomes at 2 Weeks and 6 Months After Injury



Functional outcomes quantified using Glasgow Outcome Scale-Extended for Traumatic Brain Injury (GOSE-TBI) and all injuries (GOSE-ALL) based on injury group and exposure to extracranial (EC) surgery. Additional data provided in eTable 4 for total sample sizes and mean (SD). CT⁺ mTBI indicates computed tomography-positive mild traumatic brain injury; CT⁻ mTBI, computed tomography-negative mild traumatic brain injury; GR, good recovery; MD, moderate disability; OTC, orthopedic trauma control; SD, severe disability.

These data indicate that exposure to surgery and anesthesia is associated with clinically meaningful and statistically significant decreases in functionality (GOSE-TBI and GOSE-ALL)

that are detectable at 2 weeks in the CT⁺ mTBI group and persist at 6 months. Notably, the m/sTBI group also demonstrated poorer functional outcome (GOSE-TBI and GOSE-ALL

Table 2. Regression Models for Functional and Neurocognitive Outcomes at 6 Months (Excluding Deaths Occurring Within 2 Weeks of Injury)^a

Outcome	GOSE-TBI		GOSE-ALL		Trail Making Test Part A ^b		Trail Making Test Part B	
	B (95% CI); Cohen d (95% CI)	P value	B (95% CI); Cohen d (95% CI)	P value	B (95% CI); Cohen d (95% CI)	P value	B (95% CI); Cohen d (95% CI)	P value
Injury group ^c		<.001		<.001		<.001		<.001
m/sTBI (vs CT ⁺ mTBI)	−0.85 (−1.18 to −0.52); NA	<.001	−0.80 (−1.12 to −0.47); NA	<.001	9.00 (5.07 to 12.92); NA	<.001	18.3 (5.5 to 31.0); NA	.005
CT ⁺ mTBI (vs CT [−] mTBI)	−0.03 (−0.23 to 0.17); NA	.78	0.00 (−0.20 to 0.19); NA	.96	2.47 (0.24 to 4.70); NA	.03	3.44 (−3.81 to 10.69); NA	.35
OTC (vs CT [−] mTBI)	NA	NA	0.55 (0.14 to 0.97)	.009	−0.20 (−5.32 to 4.92); NA	.94	−2.58 (−19.18 to 14.03); NA	.76
Injury group × surgery ^d		.004		.005		.54		.002
EC surgery (m/sTBI)	−1.11 (−1.53 to −0.68); −0.75 (−1.04 to −0.46)	<.001	−1.24 (−1.66 to −0.81); −0.87 (−1.17 to −0.57)	<.001	1.63 (−3.97 to 7.22); 0.13 (−0.31 to 0.56)	.57	30.1 (11.9 to 48.2); 0.70 (0.28 to 1.13)	.001
EC surgery (CT ⁺ mTBI)	−0.39 (−0.77 to −0.01); −0.27 (−0.52 to −0.01)	.04	−0.48 (−0.86 to −0.09); −0.34 (−0.61 to −0.06)	.02	2.50 (−2.10 to 7.10); 0.19 (−0.16 to 0.55)	.29	26.3 (11.3 to 41.2); 0.61 (0.26 to 0.96)	.001
EC surgery (CT [−] mTBI)	−0.27 (−0.54 to 0.00); −0.18 (−0.37 to 0.00)	.051	−0.32 (−0.59 to −0.04); −0.22 (−0.42 to −0.03)	.02	−0.93 (−3.96 to 2.09); −0.07 (−0.31 to 0.16)	.55	−1.03 (−10.86 to 8.80); −0.02 (−0.25 to 0.21)	.84
EC surgery (OTC)	NA	NA	−0.54 (−1.02 to −0.06); −0.38 (−0.72 to −0.04)	.03	−1.77 (−7.64 to 4.10); −0.14 (−0.59 to 0.32)	.56	2.92 (−16.13 to 21.96); 0.07 (−0.38 to 0.51)	.764
Age (per 10-y increase)	−0.12 (−0.17 to −0.08); NA	<.001	−0.13 (−0.17 to −0.08); NA	<.001	3.56 (3.01 to 4.10); NA	<.001	11.5 (9.7 to 13.2); NA	<.001
Sex (female vs male)	−0.25 (−0.43 to −0.08); NA	.005	−0.24 (−0.40 to −0.07); NA	.005	1.11 (−0.79 to 3.00); NA	.25	2.01 (−4.15 to 8.17); NA	.52
Race		.001		.004		<.001		<.001
Black (vs White)	−0.38 (−0.60 to −0.16); NA	.001	−0.31 (−0.51 to −0.10); NA	.004	5.67 (3.30 to 8.05); NA	<.001	30.1 (22.4 to 37.8); NA	<.001
Other (vs White)	0.17 (−0.19 to 0.52); NA	.37	0.23 (−3.48 to 4.31); NA	.18	0.41 (−3.48 to 4.31); NA	.84	2.80 (−9.84 to 15.45); NA	.66
Injury cause		.03		.01		.28		.50
Fall (vs MVC)	0.17 (−0.03, 0.37); NA	.10	0.23 (0.04, 0.42); NA	.02	−0.42 (−2.61, 1.77); NA	.71	1.04 (−6.07, 8.15); NA	.78
Other or unknown (vs MVC)	−0.17 (−0.39, 0.06); NA	.15	−0.08 (−0.29, 0.13); NA	.45	1.64 (−0.74, 4.01); NA	.18	4.63 (−3.09, 12.35); NA	.24
Educational level (per +4 y)	0.18 (0.06 to 0.29); NA	.002	0.25 (0.14 to 0.35); NA	<.001	−7.03 (−8.25 to −5.81); NA	<.001	−23.26 (−27.29 to −19.23); NA	<.001
Total ISS	0.01 (−0.01 to 0.02); NA	.24	−0.01 (−0.02 to 0.00); NA	.16	0.05 (−0.09 to 0.19); NA	.48	−0.18 (−0.63 to 0.28); NA	.44

Abbreviations: CT⁺ mTBI, computed tomography–positive mild traumatic brain injury; CT[−] mTBI, computed tomography–negative mild traumatic brain injury; EC, extracranial; GOSE-ALL, Glasgow Outcome Scale–Extended for all injuries; GOSE-TBI, Glasgow Outcome Scale–Extended for traumatic brain injury; ISS, Injury Severity Score; m/sTBI, moderate to severe traumatic brain injury; MVC, motor vehicle crash; NA, not applicable.

^a A fixed-effects linear regression model evaluated the association of injury group, surgery groups, and injury × surgery interaction, with each clinical outcome accounting for each time point separately. Standardized Cohen d effect sizes of 0.2, 0.5, and 0.8 are considered small, medium, and large effects, respectively. Because group × surgery interactions groups are in the

model, the reported main effects of injury group reflect the values in the no surgery group only.

^b Trail Making Test Parts A and B values indicate number of seconds to complete; a lower score is faster or better, and positive values represent poorer performance.

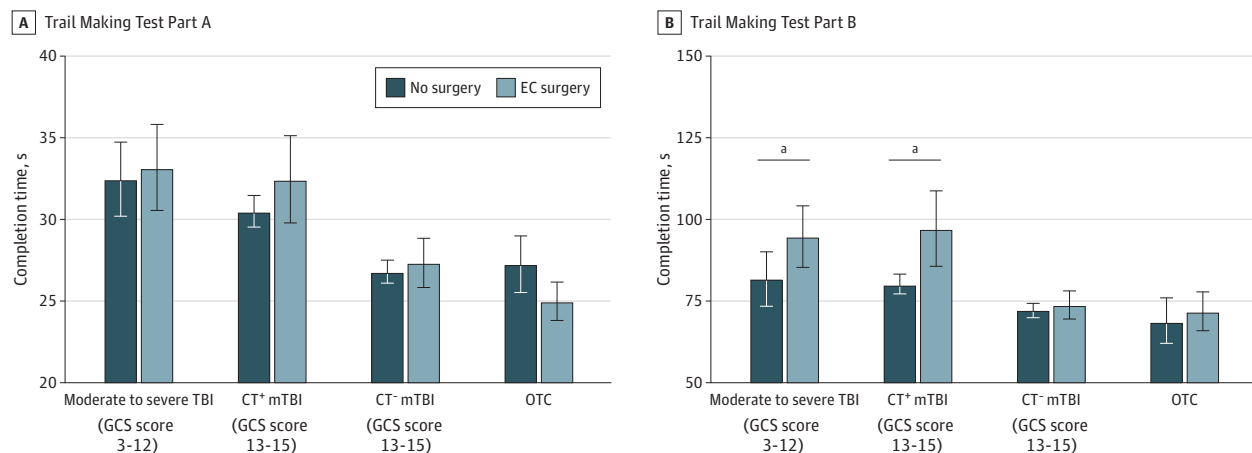
^c The main effects of the injury group presented reflect the effect in those without EC surgery.

^d Main effect of EC surgery entered in the model and is reflected in the injury group × EC surgery (CT[−] mTBI) contrasts.

scores) at 6 months. These effect sizes (approximately 0.5- to 1-point decreases in GOSE scores) reflect substantially higher disability that adversely impacts patients' quality of life. In particular, GOSE is a coarse ordinal scale on which 1-point reductions reflect major differences in independence (eg, traveling independently vs dependently and being unable to work vs working part time vs working at full capacity).³⁷ Most strikingly, in both the m/sTBI and CT⁺ mTBI groups, the effect of EC surgery at 6 months was comparable for GOSE-ALL and GOSE-TBI scores, suggesting that EC surgery may impact brain recovery after TBI (Table 2).

Due to concerns that some participants did not undergo surgical interventions because of pursuing comfort care or futility, a planned analysis of 2-week and 6-month outcomes excluded deaths before 2 weeks. This exclusion seems justified given that in the m/sTBI groups, of the total of 29 deaths that occurred within 6 months in the nonsurgical group, 26 deaths occurred at 2 weeks, a drastically different result from the 4 deaths at 2 weeks among 9 deaths within 6 months in the EC surgery group (Figure 1). After exclusion, GOSE-ALL scores were significantly lower for all EC surgery participants compared with nonsurgical participants at both 2 weeks and

Figure 2. Cognitive Outcomes at 6 Months After Injury

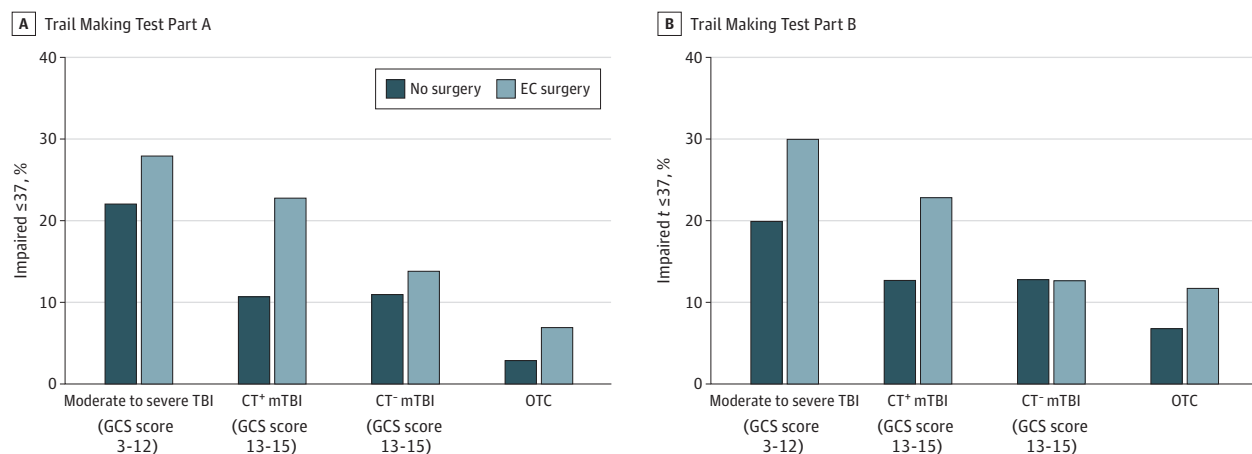


Cognitive outcomes quantified using the Trail Making Test Part A (A) and Trail Making Test Part B (B) (lower scores indicate faster or better completion times) classified by injury group and exposure to extracranial (EC) surgery. Differences were found between injury groups, which are not displayed, when assessed in the patients in the no surgery group only, which were calculated based on contrasts from the interaction regression models and regression coefficients in Table 2. Differences between injury severity in the EC surgery group were not examined because of the analysis approach. Bars are raw unadjusted means;

error bars indicate SEMs. CT⁺ mTBI indicates computed tomography-positive mild traumatic brain injury; CT⁻ mTBI, computed tomography-negative mild traumatic brain injury; GCS, Glasgow Coma Scale; OTC, orthopedic trauma control.

^a $P < .01$ for differences between nonsurgical and EC surgery groups with no adjustment for multiple comparisons.

Figure 3. Impairment on Neuropsychological Outcomes at 6 Months After Injury



Descriptive data for all cohorts grouped by exposure to extracranial (EC) surgery. Data are the percentage of participants in each group who met clinical criteria for impairment. CT⁺ mTBI indicates computed tomography-positive

mild traumatic brain injury; CT⁻ mTBI, computed tomography-negative mild traumatic brain injury; GCS, Glasgow Coma Scale; OTC, orthopedic trauma control.

6 months after injury. The lower GOSE-ALL score at 2 weeks in the EC surgical group could be from a combination of traumatic injuries, recovery from surgery, and limitations from brain injury. Lower GOSE-ALL scores at 6 months were associated with GOSE-TBI scores, again suggesting brain injury as a primary factor.

These data also show an association between exposure to surgery and anesthesia and worse neuropsychological outcomes (Trail Making Test Part B and RAVLT-LD) at 6 months after injury. The effect sizes were moderate to large for the Trail

Making Test Part B and small for RAVLT-LD. Performance on the Trail Making Test Part B was worse by 30 seconds in the m/sTBI group and by 26 seconds in the CT⁺ mTBI group. This finding translates to an absolute prevalence of impairment that is 10% greater in the EC surgery group compared with those without surgery. Performance was worse on the RAVLT-LD in the CT⁺ mTBI group but paradoxically better in the CT⁻ mTBI group who underwent surgery. Importantly, cognitive deficits were only detected in the m/sTBI and CT⁺ mTBI groups. There were no cognitive deficits in the CT⁻ mTBI or OTC groups

who underwent EC surgery, which is consistent with other studies suggesting that the general orthopedic population is not at risk.³⁸⁻⁴⁰

These findings support the hypothesis that surgery and anesthesia, or alternatively multiple trauma, might need to be included in the list of secondary insults to be avoided, if possible, to protect the brain after TBI. Substantial changes to clinical care are premature until additional studies replicate that surgery and anesthesia worsen patient-oriented outcomes after TBI. Perhaps the most immediate clinical intervention based on this study and future studies would be to screen for a recent TBI and restrict patients from undergoing elective procedures unrelated to recent traumatic injuries. Surgical procedures within 1 month after trauma are undertaken to address the injuries in 96% of cases after motor vehicle crashes, but this decreases to 60% to 88% for patients with a TBI related to sports, falls, or assaults.² Postponing surgery is a costly proposition that has implications for the patient, surgeon, and economy but is necessary in certain circumstances.^{41,42} Surgery is pursued after a traumatic event to mitigate the natural consequences that threaten life or limb, so the risk to benefit ratio will often favor surgical intervention. The data presented here suggest that patients at highest risk after TBI are in the CT⁺ mTBI to m/sTBI range. The participants with CT⁻ mTBI or OTC who underwent surgery did not have worse outcomes at 6 months, aside from GOSE-ALL, which is reassuring because a CT⁻ mTBI diagnosis is more likely to be overlooked due to subtle signs and symptoms.^{43,44}

These data prompt numerous questions regarding potential mechanisms for neuronal vulnerability after TBI. Although secondary insults from surgery and anesthesia are possible, numerous preclinical studies support nonmodifiable, biologically plausible mechanisms that contribute to TBI outcomes, including tauopathy,^{25,26,45,46} age, and polymorphisms of genes controlling cell water permeability and oxygen sensing.^{47,48} There are limited interventions during the perioperative period that can improve patient-oriented outcomes beyond encouraging prehabilitation and avoiding medications, such as benzodiazepines and centrally acting cholinergics, known to contribute to postoperative neurocognitive disorders.^{10,49,50} Additionally, although exposure to anesthesia affects neuronal development in the preponderance of animal models,⁵¹ the studies are heterogeneous and difficult to extrapolate to humans.⁵² Clinical studies have investigated differential effects of anesthetics on inflammatory markers⁵³ and cerebrovascular responses,⁵⁴ yet general anesthesia produces similar outcomes on neurocognitive tests and confusional states compared with regional or neuraxial anesthesia,^{38-40,55,56} suggesting that the surgical stress response⁵⁷ and patient-specific factors may be the primary contributors to neurologic changes. Age and preexisting cognitive deficits are the most consistent individual risk factors for postoperative neurocognitive disorders,^{58,59} including delirium or prolonged postoperative cognitive dysfunction. The link between surgery and postoperative neurocognitive disorders is strong enough that some have proposed it warrants specific informed consent.^{10,60,61}

Limitations

The main limitation of this study is the concern for confounding by indication (ie, the surgical group had worse outcomes despite similar presentations because of more severe traumas or brain injuries or an interaction with peripheral injury or multiple trauma).⁶² Other examples of this phenomenon^{63,64} need to be addressed with well-designed studies. We minimized the potential for confounding by emphasizing comparisons of surgery and no-surgery groups within TBI severity subgroups and a non-TBI orthopedically injured group, by controlling for relevant confounds, and by including outcomes that were relatively brain injury specific, such as GOSE-TBI and cognitive performance measures. Although multivariable analysis supported that outcomes were worse in the surgery and anesthesia-exposed group compared with the non-surgical TBI group after controlling for age, sex, race, educational level, and time to ED, it remains possible that covariates influenced the results, especially loss of consciousness, posttraumatic amnesia, cause of injury, ward vs intensive care unit admission, total injury severity score, peripheral injury severity score, and number of operations because they were not balanced after propensity weighting for group imbalance and missingness. Other unquantified variables also could have affected the study; for example, factors that could not be controlled for included insults introduced intraoperatively or during transportation (eg, to acquire imaging), surgical urgency,⁴ American Society of Anesthesiologists Physical Status, delirium,⁶⁵ anesthetic type, specific drugs, doses, or drug timing. Notably, participants whose only surgery was a tracheostomy tube, gastrostomy tube, or both were excluded because in isolation those operations are reflective of TBI severity. Inclusion of those participants would have biased the results in favor of our hypothesis. If patients underwent a different EC surgery and a tracheostomy or gastrostomy, then they were kept in the EC surgery group. Variables associated with injury severity, morbidity, and mortality in trauma patients, namely presenting shock index,⁶⁶ hemoglobin,⁶⁷⁻⁶⁹ hypoxemia, and base deficit,⁷⁰⁻⁷² were compared between nonsurgical and EC surgery groups. Differences in presenting shock index, hemoglobin concentrations, hypoxemia, and base deficit were not statistically significant between the EC surgery and nonsurgical groups within the same TBI severity and therefore are unlikely to be confounding variables, so they were not included in the models. Base deficit data were mostly missing, presumably because the laboratory tests were not clinically necessary. Base deficit generally worsens outcomes when greater than 6 to 10, which is higher than for most participants in this study.⁷³⁻⁷⁵ We acknowledge that the use of GOSE as early as 2 weeks after injury is uncommon and its fitness for early assessment (such as when participants are inpatient) is debated.^{76,77} In the current sample, 89% of participants were discharged by 2 weeks after injury, and reporting both 2-week and 6-month GOSE data was important to describe participant trajectories. Also, the results in these EC surgery participants are not generalizable to other populations, in particular intracranial surgery, given that the benefits of such procedures would presumably far outweigh any harmful effects of surgery and anesthesia on outcomes.

Additionally, this study did not assess the impact of type or number of operations, anesthesia time, or the critical window of exposure. Future studies are warranted to test these and other intraoperative variables in patients with TBI, but prior studies on postoperative neurocognitive disorders have found that the type of surgery and anesthesia did not affect the outcomes.^{55,78} This finding is consistent with the idea that vulnerable patient populations are at risk, but not the general population.⁷⁹ The time frame of surgery here was primarily within 5 days after TBI but extended up to 20 days. The critical window of vulnerability after TBI could span several weeks given sustained changes in blood-brain barrier permeability, edema, inflammatory processes, and intracellular and extracellular signaling.⁸⁰ Determining how long elective procedures should be delayed after TBI is not a trivial task, but blood-based biomarkers^{81,82} could individualize the decision to proceed with or delay surgery. Interestingly, cardiac surgery

alone increases biomarkers indicative of brain injury.⁸³ Biomarkers may also be useful in determining surgical timing in nonelective cases, which is a complicated decision weighing the peripheral trauma against TBI stability.

Conclusions

The findings of this cohort study warrant further investigation regarding the clinical implications and mechanisms before changing current clinical care. Nevertheless, these are the first data in humans, to our knowledge, that suggest EC surgery and anesthesia might need to be included in the list of secondary insults after TBI. Likewise, TBI might need to be included in the list of nonmodifiable patient factors, along with age and preclinical or diagnosed dementia, that increase the risk for postoperative neurocognitive disorders.

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Invited Commentary

Surgery, Anesthesia, and TBI Outcomes—Unraveling the Complex Interplay

Caitlin R. Collins, MD, MPH; Andre Campbell, MD

In their study “Extracranial Surgery and Functional and Cognitive Outcomes After Traumatic Brain Injury: A TRACK-TBI Study,”¹ Roberts et al shed crucial light on the potential risks associated with extracranial surgery in patients with traumatic brain injury (TBI). Their



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research provides a necessary foundation for a more informed risk-benefit analysis regarding surgery in these patients. While the majority of extracranial operations studied were related to the traumatic injury (and therefore likely urgent and necessary), we agree that TBI should be explicitly highlighted as a nonmodifiable risk factor for postoperative neurocognitive disorders during informed consent discussions. Additionally, delaying any nonurgent surgical intervention for patients with moderate to severe TBI or for patients with mild TBI and positive results of computed tomography of the head should be strongly considered.

One area warranting further examination remains the potential influence of anesthetic techniques on postoperative outcomes for patients with TBI. Although Roberts et al¹ reference prior studies²⁻⁴ indicating no significant difference in postoperative neurocognitive disorders based on anesthetic technique, it is important to note that many of these studies focused on older populations undergoing a heterogeneous array of procedures. Because most patients with trauma are young and have fewer preexisting medical comorbidities than most studied surgical populations, they represent a dis-

tinct population worth individual evaluation. These prior studies²⁻⁴ also often compared general anesthesia vs epidural anesthesia, which can produce similar, detrimental hemodynamic changes. Because many of the extracranial operations were for extremity fractures, peripheral nerve blocks may represent a more appealing comparison with general anesthesia given their more limited associations with hemodynamic parameters.

Future attempts to clarify the interplay between surgery or anesthesia and neurocognitive outcomes in patients with TBI should include both full neuropsychological testing to further delineate the cognitive impact and intraoperative data. Hypotension and hypoxemia are well-established secondary insults that result in worsened neurologic outcomes. These vital signs are also closely monitored intraoperatively and are typically captured in the electronic medical record. It is crucial to consider their potential impact on the observed outcomes. Further analyses should aim to control for prolonged episodes of intraoperative hypotension or hypoxemia to minimize the potential for conflating surgery or anesthesia with previously well-described harms in patients with TBI.

Roberts et al¹ masterfully elucidate the nuanced interplay between surgery, anesthesia, and TBI. While the avenues for further inquiry and elucidation remain vast, this study lays the groundwork for further investigation, offering a platform for refining and optimizing the care of patients with TBI undergoing extracranial surgery.

ARTICLE INFORMATION

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